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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GUCKER, STEPHEN	

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 05/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/063,569	GODDARD ET AL.	
	Examiner	Art Unit	
	Stephen Gucker	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 February 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-8 and 11-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-8, 11-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Response to Amendment

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. Any objections or rejections made in a previous Office Action that are not herein reinstated have been withdrawn.

3. Claims 4-8 and 11-17 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a well-established utility or a disclosed specific and substantial utility for reasons of record and the following. The instant application puts forth the assertion that the claimed isolated proteins are useful for the diagnosis and treatment of disease states. The disclosure proposes that the diagnosis of disease states by the claimed proteins can occur through detection of the claimed proteins in biological samples by various binding assays, such as those assays that would use antibodies raised against the claimed proteins. Assays used to detect the claimed proteins or fragments or portions of them, such as a signal sequence or an extracellular domain, are asserted to be useful in disease diagnosis. Signal sequences are a portion of the protein amino acid chain, usually at the N-terminus, that function to indicate to the internal cellular machinery that the proteins bearing such signal sequences are intended to be exported or secreted from the interior of the cell to the exterior of the cell, outside of the cell membrane. Such signal sequences are usually deleted or "clipped" from the N-terminal region of the amino acid chain by enzymatic action to produce what is normally called a "full-length or mature" protein before the mature protein is actually secreted or exported from the cell. Alternately, signal sequences may also indicate to

the cell that the protein is to be inserted or "threaded" into a lipid bilayer, such as the cell membrane, where the protein may function as a cellular ligand or receptor for external ligands or soluble receptors such as cytokines, neurotransmitters, hormones, or hormone binding proteins. In which case, the protein may be divided into an extracellular domain, a transmembrane domain, and a cytoplasmic domain, depending upon where that portion of a protein's chain of amino acids reside, relative to the lipid bilayer of the cell membrane. The specification also discloses that the claimed proteins could be used to screen for agonist or antagonist compounds (small organic molecules or other peptides/proteins) that either potentiate or inhibit the activity of the claimed proteins. The specification argues that the claimed proteins could be used as pharmaceuticals directly or that variants of the claimed proteins such as fusion proteins, immunoadhesins, chimeras, covalently-linked proteins, or the claimed proteins with amino acid substitutions, additions, or deletions could be used as pharmaceuticals. Furthermore, the instant application puts forth the assertion that the claimed proteins could be used as molecular weight markers for protein electrophoresis or that their presence or absence could be used for tissue typing biological samples. The claimed proteins could be used to screen for pharmaceuticals that bind to the proteins or that may activate or inhibit the activity of the proteins in order to bring about a therapeutic effect. Alternately, biological samples could be screened against the encoded proteins to see if they contained compounds that either activated or inhibited the activity of the encoded proteins, or to determine what ligands or receptors interacted with the encoded proteins to produce biological effects. These activations and inhibitions could be

screened by direct binding or by measuring protein-protein interactions such as in the yeast-based genetic system. Likewise, antibodies and modified antibodies (chimeric antibodies, humanized antibodies, covalently-linked antibodies, immunoconjugates, etc.) to the proteins could be used to bind to the proteins and either potentiate or inhibit the activity levels of the proteins. In lieu of using the actual proteins themselves in screening assays, the specification also postulates that the proteins or various types of antibodies to the proteins could be studied by a combination of x-ray crystallography and computer modeling to produce structural analogs to the proteins or antibodies by the process of rational drug design. The instant application also teaches that antibodies that bind to the proteins could be used to isolate or purify the proteins, or detect the presence of the proteins in a biological sample. Finally, Applicant teaches that transgenic animals could be used as a source of the claimed proteins.

Upon searching and examination, it is the Examiner's position that the claimed genus of proteins, variants of the proteins, and fragments or portions of the proteins, based on SEQ ID NO:63 (the encoding nucleic acid sequence) or SEQ ID NO:64 (the amino acid sequence, otherwise known as PRO3566), do not have a well-established utility known in the prior art because the application has not identified any well-established utility that is particular to PRO3566, and the Examiner has not found any such utility in the prior art of record. Furthermore, the instant disclosure does not provide a specific utility for that which is claimed for the following reasons. Applicant asserts that the PRO3566 proteins could be used as molecular weight markers for protein electrophoresis. This would be true for all proteins of the same molecular weight

as the PRO3566 protein, and this is not a specific utility. The specification teaches that the PRO3566 protein will provide guidance to those employing computer modeling techniques in place of x-ray crystallography, but this utility is true of any protein in general and is not specific to the protein of the instant Application. Applicant asserts that the PRO3566 sequences could be used for tissue typing, but Applicant provides no teachings as to what types of normal tissue PRO3566 can be found in, or that PRO3566 is limited to any particular type of tissue. It is also noted that every tissue type of the body produces its own specific markers, so again, this asserted utility is not specific.

The instant disclosure is silent as to the actual biological activity or function of PRO3566. Without some minimal teaching as to the amount or level of activity of PRO3566 in either a normal or disease state, the artisan is without guidance or direction as to what any change in amount or level of activity of PRO3566 would indicate and what therapeutic course of action should follow. For example, it is completely unknown as to what a rise in the level or activity of PRO3566 proteins would indicate in a cancerous tissue. Would a rise in PRO3566 indicate that an increased level or activity associated with cancer meant that the activity or function of the PRO3566 proteins needed to be suppressed, under the assumption that PRO3566 was somehow causative or contributory to the pathology of cancer? Or would a rise in PRO3566 indicate that the tissue was attempting to combat the cancer by turning on or activating cancer suppressing genes? (An example known in the art of a cancer suppressing gene is p53). In which case, the artisan would desire to further increase the activity or level of PRO3566 and not suppress or inhibit it. Because the instant application does not

provide some minimal context as to what altered levels of PRO3566 mean, up or down, the artisan can find no therapeutic utility for the claimed proteins because significant and substantial further research would need to be performed in order to answer these simple but vital questions. Without an answer to these vital questions, not only do the PRO3566 proteins have no substantial therapeutic utility, but the antibodies to the protein have no substantial therapeutic utility as well because no meaningful therapeutic administration of the PRO3566 proteins or antibodies can be accomplished without the minimal knowledge of whether increased or decreased levels or activities of PRO3566 was a deleterious or beneficial biological event.

In regards to the asserted utilities of using the PRO3566 proteins and antibodies to the proteins for screening assays to find drugs or endogenous ligands, receptors, or other compounds that interact with or bind to PRO3566, without some minimal knowledge as to the function or significance of PRO3566 in a biological context, said asserted utilities are not substantial because significant further research would have to be performed in order to know why or for what purpose the artisan would want to activate or inhibit the biological function of PRO3566 in the first place. In other words, without at least some knowledge as to the function or activity of PRO3566 in either normal or diseased tissue (the disclosure is silent to both), the artisan has no substantial utility for any of the substances that interact with PRO3566 in an assay until substantial further research is conducted that reveals the biological utility of PRO3566 itself. And without this knowledge, transgenic animals lacking PRO3566 or genetically engineered to produce PRO3566 also have no substantial utility because substantial

further research would have to be performed in order to bestow upon such animals a biological utility in the context of a research animal model of a disease state or a method of PRO3566 production.

In regards to the asserted diagnostic utility of PRO3566 proteins, the same reasoning that applied to the lack of substantial therapeutic utility would also apply to a showing of a lack of substantial diagnostic utility. Without a minimal knowledge as to what an appropriate level or activity of the PRO3566 proteins are in healthy normal appropriate control tissue and how they would differ in pathological tissue afflicted with specific diseases, the finding of the absence or presence of PRO3566 proteins in tissue does not provide artisans with any workable information they could act on in a diagnostic fashion because the instant disclosure does not present a persuasive case that PRO3566 sequences are significantly altered in any way in any pathology. The only working example in this regard offered by the specification indicates that PRO3566 mRNA is more highly expressed in a normal skin sample than in a melanoma tumor sample and is more highly expressed in an esophageal tumor sample than in a normal esophagus sample. Applicants further argue that a change in the level of mRNA for a particular protein generally leads to a corresponding change in the level of the encoded protein. Applicants refer to a declaration of J. Chistopher Grimaldi (Exhibit 1, filed 5/16/05) and argue that the biological significance of the data, or the role of PR03566 in cancer, "is not necessary to use the claimed polypeptides as cancer diagnostic tools" (p. 22-23 of the response filed 4/11/05). Applicants argue that Exhibit 1 teaches that the DNA libraries used in the gene expression studies were made from

pooled samples of normal and of tumor tissues. Grimaldi states in section 6 that "I conducted a semi-quantitative analysis of the expression of the DNA sequences of interest in normal versus tumor tissues. Expression levels were graded according to a scale of +, -, and +/- to indicate the amount of the specific signal detected. Using the widely accepted technique of PCR, it was determined whether the polynucleotides tested were more highly expressed, less expressed, or whether expression remained the same in tumor tissue as compared to its normal counterpart. Because this technique relies on the visual detection of ethidium bromide staining of PCR products on agarose gels, it is reasonable to assume that any detectable differences seen between two samples will represent at least a two fold difference in cDNA."

Furthermore, in another declaration of J. Christopher Grimaldi (Exhibit 4), Grimaldi states that when a gene is overexpressed, the gene product or polypeptide will also be overexpressed (p. 19 of response). The declaration of Dr. Paul Polakis avers that mRNA levels typically correlate with an increase in abundance of the encoded protein (p. 20 of response). Applicants further cite Orntoft et al., Hyman et al., and Pollack et al. in support of the argument that in the vast majority of cases, the combined teachings of the art teach that gene amplification influences gene expression and that gene expression influences protein levels. In addition, Applicants refer to the declaration of Dr. Ashkenazi and cited references Hanna and Mornin who teach that even if higher levels of mRNA do not correlate with an increase in abundance of the encoded protein, that type of information is also useful in diagnosing and treating patients. Applicants'

arguments have been fully considered but have not been found to be persuasive. A utility of being a diagnostic target for melanoma or esophageal tumors is a utility that requires or constitutes carrying out further research to identify or reasonably confirm a "real world" context of use. This is not a substantial utility. In Example 30, Applicants teach that PRO3566 was overexpressed in normal skin and esophageal tumor than in melanoma tumor and normal esophagus tissue. There is no guidance in the specification as to how high the levels of overexpression are. There is no information in the specification as to the differences in expression or whether the results were statistically significant. Applicants have provided no indication of the nature or number of samples that were used. The declaration of Grimaldi does not teach the level of reproducibility or the level of reliability of the results. If a clinician took a skin or esophageal tissue sample from a patient with suspected melanoma or esophageal cancer, what is the likelihood that when compared with normal tissue, the level of PRO3566 from the patient would be higher or lower? How many samples would be needed? What sensitivity would be needed? Applicants have provided no indication of the nature or number of samples that were used.

The only thing Applicants teach is that the gene was "more highly expressed," and this does not enable the skilled artisan to differentiate amongst expression levels in order to diagnose any diseases. On p.19 of the response, Applicants state that when a gene is overexpressed, the corresponding protein will generally also be overexpressed. However, Chen et al. teach that the correlation between protein levels and mRNA expression can vary depending upon the protein (Chen et al. (2002), Mol. Cell.

Proteomics 1.4: 304-313). Of 165 protein spots studied by Chen et al., only 17% of the samples showed a statistically significant correlation between mRNA and protein (p.311). Some of the proteins actually demonstrated a negative correlation with the mRNA expression values (p.311). One skilled in the art would need to do further research to determine whether or not the PRO3566 polypeptide levels increased or decreased significantly in the tumor samples. Such further research requirements make it clear that the asserted utility is not yet in currently available form, i.e. it is not substantial. Without more specifics about necessary sample size, expression level range for normal and tumor tissues, types of skin and esophageal tissue that can be used, and other questions, the specification has not provided the invention in a form readily usable by the skilled artisan such that significant further experimentation is unnecessary. Besides all of the aforementioned information that the skilled artisan would need to know in order to provide the instant invention with readily available "real world" utility, other confounding variables would have to be controlled for, such as patient age, gender, pharmaceuticals taken, general health, smoker versus nonsmoker, etc. in order to make a valid comparison between a normal tissue sample and a cancerous tissue sample. For example, suppose PRO3566 sequences increase with the age of the patient. Then, the results of the only working example could simply mean that the normal skin sample tested was simply older than the melanoma sample, and the normal esophagus sample is simply younger than the esophageal tumor sample. Because absolutely no biological function at all has been associated with any of the PRO3566 sequences, the skilled artisan cannot make any useful determination as to

what differences in expression would be indicative of any healthy or diseased tissue because the PRO3566 sequences may be present in different amounts simply by chance or be present in different amounts in different samples because one sample has more male than female tissue, or one sample had a patient taking aspirin or some other drug that altered the level in comparison to the other sample, or more smokers contributed to one sample than the other sample, etc.

Applicant's arguments filed 8/17/05 have been fully considered but they are not persuasive because Applicant argues that the Examiner dismisses the data from Example 18 and has taken the opposite position in a related application. This is unconvincing because every application must stand or fall on its own merits, and claims to nucleic acids (the related application) and to proteins (the instant application) are not equivalent. Furthermore, the Examiner has not dismissed the data from Example 18, but has merely pointed out that it is not well-established in the art that a change in the level of mRNA for a particular protein generally leads to a corresponding change in the level of the encoded protein (the instant invention), especially in cancerous tissue, as taught by Chen et al., already of record. Therefore, the Applicant's assertion that a polypeptide is differentially expressed in tumor cells based on a difference in expression in the encoding nucleic acids has definitely not been demonstrated by the teachings of the instant application or of the prior art of record. Even if the Examiner were to concede that different levels of mRNA in a tumor sample lead to different levels of the encoded polypeptide (which the Examiner has not conceded), Applicants have still failed to provide a convincing argument that the PRO3566 polypeptide has any relationship at all

to cancer, and not to sample age, gender, drug use, smoking, normal random distribution, etc. as set forth above. Because all of these confounding variables are not discussed at all in the instant application, Applicant's arguments drawn to relative levels of PRO3566 mRNA between normal tissue and diseased tissue in contrast to absolute levels are moot; the differences in relative levels could still be attributed to any one or more of the confounding variables previously mentioned, and the instant invention would be totally incapable of achieving any useful result as envisioned by the instant disclosure. In contrast to Applicant's arguments where Applicant implies that the Examiner is maintaining the rejection because the PRO3566 polypeptide has not been shown to be useful in every melanoma or esophageal tumor diagnosis, the Examiner queries Applicants to show that the PRO3566 polypeptide has been shown to be useful in any single diagnosis of melanoma or esophageal tumor. Quite simply, the PRO3566 polypeptide has not been shown to be present in different amounts between any normal tissue and its corresponding tumor!

Concerning Applicant's arguments directed toward the Chen et al. reference, Applicant appears to be agreeing with the Examiner's position when Applicant notes that Chen reports that the overwhelming majority of genes examined (77 out of 98), do not show a statistically significant correlation between protein and mRNA expression. Applicant's "cherry-picking" of three genes that do show a correlation (Chen et al.'s Figures 2A-2C) do not support Applicant's contention that more likely than not, any PRO polypeptide would follow such a correlation between normal and cancerous tissue. Indeed, the whole thrust of the experiments of Chen et al. is, in fact, that such a positive

correlation between mRNA and protein levels in cancerous tissue, more likely than not, does not exist! Applicant's criticism of Chen et al. based on Chen's citation of Celis et al. (page 311) is unconvincing because Celis et al. was studying 40 well resolved abundant proteins of bladder cancer, and the instant disclosure does not teach that PRO3566 polypeptide can either be (1) well resolved by any method, or (2) be an abundant protein in any cancer. In fact, if one is to believe Applicant's assertions, PRO3566 polypeptide is less abundant in cancer (melanoma) than it is in normal skin.

Finally, to again address Applicant's position that mRNA and polypeptide amounts go hand-in-hand, the Examiner introduces a study of a 'meta-dataset' performed by Greenbaum et al. Greenbaum et al. combined various datasets to examine protein abundance information for approximately 2,000 proteins, or, the term they use, ORFs (open reading frames). No significant correlations were found globally between the amounts of mRNA found, and the amounts of the encoded proteins expressed (page 117.4), and multiple reasons for the absence of said correlations are given (again, starting on page 117.4). Once again, this large 'meta-dataset' study supports the Examiner's position that unless something (and not everything, as Applicant argues) is known about the biological significance or function of the encoded protein, such as its cellular localization, or knowledge that the protein is a member of a stoichiometric subset of proteins, etc., like Greenbaum et al. teach throughout this reference, the knowledge of the amount of an encoding nucleic acid does not automatically bestow the knowledge of the amount of the encoded protein present until considerable further research and experimentation on the significance and function of

some biological aspect of the protein itself is performed, which is lacking in the instant application in regards to PRO3566 polypeptides.

Applicant's arguments filed 2/16/06 have been fully considered but they are not persuasive because Applicant argues that Chen examined tissues in different stages of normal or cancerous growth, that the relationship between mRNA and protein expression was determined by using the average expression value for all samples, and an arbitrary threshold was chosen for the correlation to be considered significant; that accordingly, the reference does not take into account for different expression in different tissues or different stages of cancer, that no attempt was made to compare expression levels in normal versus tumor samples, and that Chen does not address whether increased mRNA levels in tumor samples taken together as one group correlated with increased protein protein levels in tumor group versus normal tissue. This argument is not persuasive for the following reasons. First, Chen, unlike the present application, indeed tested corresponding normal tissues (the abstract and page 308). Second, unlike the present application, Chen's results and conclusions are based on statistical analysis (pages 306 and 310). Therefore, Chen convincingly demonstrates the lack of correlation between mRNA and protein, at least in certain tumor tissues. In contrast, Applicant's argument is merely based on opinions, and Applicant provides no evidence to support such a correlation even if the data were significant. As such, "more likely than not" is not established in the instant application.

4. Claims 4-5 and 12-17 are rejected under 35 U.S.C. 1 12, first paragraph, because the specification, were it enabling for an isolated polypeptide comprising SEQ

ID N0:64, would still not reasonably provide enablement for polypeptides having at least 95% or 99% amino acid sequence identity to the polypeptide of SEQ ID NO:64 and is maintained for reasons of record and the following. Applicants argue that one skilled in the art would know how to make and use the claimed polypeptides, and Applicants have disclosed how to determine if the claimed polypeptides or encoding nucleic acids are differentially expressed in melanoma tumors or esophageal tumors compared to normal skin or normal esophagus (p. 27). Applicants' arguments have been fully considered but have not been found to be persuasive. Being differentially expressed in melanomas or esophageal tumors is not a functional limitation. Rather, it is a characteristic of an individual sequence. Even if the specification provided support for diagnosing melanomas or esophageal tumors with PR03566, the skilled artisan would not know how to use polypeptides having sequences at least 95% or 99% sequence identity to PRO3566. Such sequences are not taught to be differentially expressed in melanomas or esophageal tumors. One skilled in the art would not know how to engineer a sequence such that it is overexpressed in certain tissues. Claims 14-17 have the limitation "wherein said isolated polypeptide or a fragment thereof can be used to generate an antibody which can be used to specifically detect the polypeptide of SEQ ID NO:64 in skin tissue or esophagus samples." Again, this is not a functional limitation. Applicants have not specified certain regions of SEQ ID NO:64 which contain epitopes particular to an anti-PRO3566 antibody. This is merely another means for claiming a polypeptide having a percent identity to SEQ ID NO:64. One skilled in the art would not know how to make a protein at least 95% or 99% identical to SEQ ID NO:64 such that

antibodies raised against the sequence would specifically recognize SEQ ID NO:64 and not other sequences 95% or 99% identical to SEQ ID NO:64.

Applicant's arguments filed 8/17/05 have been fully considered but they are not persuasive because Applicant argues that one of skill in the art would know how to make and use variants of PRO3566 within 95% or 99% sequence identity. However, Applicant fails to address the Examiner's position that no variant nucleic acid encoding even a single polypeptide variant sharing 95% or 99% sequence identity with PRO3566 has been taught by the instant specification, either in a normal tissue sample or a cancerous one. Applicant has provided no teachings or evidence that variants of PRO3566 polypeptide having 95% or 99% sequence identity are differentially expressed, or even exist, in any tissue, healthy or diseased, so the disclosure is not commensurate in scope with, and cannot enable, the claimed invention.

Applicant's arguments filed 2/16/06 have been fully considered but they are not persuasive because Applicant argues that a variant is useful to make an antibody to a native PRO3566 epitope. However, Applicant has not provided a convincing argument that specific certain regions of SEQ ID NO:64 contain epitopes which would be particular to an anti-PRO3566 antibody. This is merely another means for claiming a polypeptide having a percent identity to SEQ ID NO:64. Also, Applicant's have not demonstrated that the PRO3566 protein is differentially expressed in any tissue type, healthy or not, in order to make it an enabled diagnostic.

5. The rejection of claims 4-5 and 12-17 under 35 U.S.C. 112, first paragraph, for failing to comply with the written description requirement, is maintained for reasons of

record and the following. Applicants argue that the claimed polypeptides are not defined only by sequence identity, but that they now recite specific functional limitations that the polypeptide is more highly expressed in normal skin and esophageal tumor than in melanomas or esophagus or the polypeptides can be used to raise antibodies that recognize SEQ ID NO:64. Applicants argue that based on the high percentage of sequence identity and the described method of detecting and quantifying overexpression in tumors, one skilled in the art would have known at the time of the invention that Applicants had possession of the claimed polypeptides. Applicants' arguments have been fully considered but have not been found to be persuasive. As stated above, the claims have no functional limitations. In addition, the specification does not provide a utility or function for PRO3566. The claimed polypeptide sequences may have functions and structures which differ greatly from that of PRO3566, and therefore one of skill in the art would not be able to predictably identify the encompassed molecules as having the same functional limitations to those instantly claimed.

Applicant's arguments filed 8/17/05 have been fully considered but they are not persuasive because Applicant argues that mere sequence identity (95% or 99%) bestows upon the claimed invention all of the functional limitations recited in the instant claims. This is unpersuasive because functional limitations cannot be predicted from a protein's amino acid sequence (see Rudinger, especially page 6). Without a more adequate written description of which amino acids in the PRO3566 sequence bestow upon itself its recited functional limitations (presence in various tissues, ability to make

specific antibodies to SEQ ID NO:64), these instant claims lack an adequate written description. For instance, a polypeptide sharing 95% amino acid sequence identity with SEQ ID NO:64 would be capable of being used to make antibodies not only specific to SEQ ID NO:64, but also specific to its own sequence and a great many related sequences..

Applicant's arguments filed 2/16/06 have been fully considered but they are not persuasive because In re Wallach concerns different degenerate nucleic acids that encode an identical polypeptide, and not the situation here, where Applicant is claiming different, non-degenerate nucleic acids that encode different polypeptides.

5. Claims 4-8 and 11-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility, or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

6. Claims 14 and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Janer et al. and is maintained for reasons of record and the following. Applicants argue that Janer et al. do not provide the amino acid sequence of SEQ ID NO:64 and Janer et al. do not describe the coding region of the sequence that encodes SEQ ED NO:64 (p. 31 of the response). Applicants' arguments have been fully considered but have not

been found to be persuasive. The sequence as taught by Janer et al. encodes a polypeptide 98% identical to SEQ ID NO:64. This is an inherent feature of the sequence as taught by Janer et al.

Applicant's arguments filed 8/17/05 have been fully considered but they are not persuasive because Applicant argues that the sequence of Janer does not "necessarily and always" encode a polypeptide according to the instant claims. However, it is the Examiner's position that because the claims recite "wherein said isolated polypeptide or a fragment thereof" (underlining mine) can be used to generate an antibody..., such claim language which encompasses a fragment of Janer meets all the limitations of the claim, and said fragment would "necessarily and always" encode a polypeptide capable of being used to raise antibodies to SEQ ID NO:64, because the fragment lacks the extra nucleotides that would produce a frameshift as argued by Applicant. Because Janer's sequence does not match the instant invention exactly, it meets the limitations of being "heterologous" to instant SEQ ID NO:64, meeting the limitations of claim 16.

Applicant's arguments filed 2/16/06 have been fully considered but they are not persuasive because Applicant has not specifically and explicitly indicated where the prior art fails to meet a claim limitation. Instead, Applicant asserts that the prior art must meet the limitations of a), b), and c), whereas the claims read a), b), or c) in the alternative. Applicant fails to indicate why a fragment of the prior art protein could not meet the claim limitations.

7. No claim is allowed.

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Technical Center 1600 general number which is (571) 272-1600.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Gucker whose telephone number is (571) 272-0883. The examiner can normally be reached on Monday to Friday from 0930 to 1800. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, can be reached at (571) 272-0867. The fax phone number for this Group is currently (571)-273-8300.

Stephen Gucker

May 1, 2006

JANET L. ANDRES
SUPERVISORY PATENT EXAMINER